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Roth, P ; Wick, W ; Weller, M

Abstract: PURPOSE OF REVIEW: Glucocorticoids are frequently used in the treatment of patients with neurooncological disorders. This review addresses different clinical indications and provides information on beneficial and undesired effects exerted by these drugs. The most important cellular mechanisms of action of glucocorticoids under different conditions are highlighted. RECENT FINDINGS: Glucocorticoids have been used for the treatment of lymphoid neoplasms for decades. In addition to proapoptotic effects, recent studies have delineated the induction of autophagy in lymphoma cells as an important alternative mode of cell death. In contrast, glucocorticoids may reduce the sensitivity of tumor cells, including glioma cells, other than lymphoma cells to chemotherapeutic agents. Corticosteroids also provide transient relief from neurological symptoms caused by increased intracranial pressure and edema associated with primary and secondary brain tumors. However, treatment with glucocorticoids is also commonly associated with considerable side-effects including hyperglycemia, myopathy, osteoporosis, lymphopenia and others. SUMMARY: Although in clinical use for more than 40 years in the field of neurooncology, steroids remain a central and essential part in the treatment of brain tumor patients. Along with improved therapeutic options and prolonged life expectancy of many of these patients, careful administration is required and long-term side-effects must be considered.

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Steroids in neurooncology: actions, indications, side effects

Patrick Roth^{1*}, Wolfgang Wick², Michael Weller¹

Affiliations:

¹Department of Neurology, University Hospital Zurich, Switzerland, ²Department of Neurooncology, Neurology Clinic and National Center for Tumor Disease, University of Heidelberg, Germany

*Correspondence: Dr. Patrick Roth, Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland, Tel.: +41 (0)44 255 5511, Fax: +41 (0)44 255 4380, E-mail: patrick.roth@usz.ch

Keywords: glucocorticoid, brain tumor, edema

Abstract

Purpose of review: Glucocorticoids are frequently used in the treatment of patients with neurooncological disorders. This review addresses different clinical indications and provides information on beneficial and undesired effects exerted by these drugs. The most important cellular mechanisms of action of glucocorticoids under different conditions are highlighted.

Recent findings: Glucocorticoids have been used for the treatment of lymphoid neoplasms for decades. In addition to pro-apoptotic effects, recent studies have delineated the induction of autophagy in lymphoma cells as an important alternative mode of cell death. In contrast, glucocorticoids may reduce the sensitivity of tumor cells, including glioma cells, other than lymphoma cells to chemotherapeutic agents. Corticosteroids also provide transient relief from neurological symptoms caused by increased intracranial pressure and edema associated with primary and secondary brain tumors. However, treatment with glucocorticoids is also commonly associated with considerable side effects including hyperglycemia, myopathy, osteoporosis, myopathy, lymphopenia and others.

Summary: Although in clinical use for more than 40 years in the field of neurooncology, steroids remain a central and essential part in the treatment of brain tumor patients. Along with improved therapeutic options and prolonged life expectancy of many of these patients, careful administration is required and long-term side effects must be considered.

Introduction

Steroid hormones include the sex steroids such as androgens, estrogens and progestagens as well as the mineralocorticoids and glucocorticoids. The latter are referred to as “steroids” in clinical language use in oncology and have a multitude of functions that can be therapeutically exploited in tumor patients. Naturally occurring glucocorticoids in humans comprise cortisol (alternative name: hydrocortisone) and corticosterone which are produced by the adrenal gland. They are involved in various physiological conditions such as carbohydrate and protein catabolism, stress and immune responses and the regulation of inflammation and electrolyte levels in the blood [1].

Glucocorticoids bind to the glucocorticoid receptor which is located in the cytoplasm. Subsequently, the receptor-ligand complex translocates into the nucleus where it binds to glucocorticoid response elements which are located in the promoter region of target genes. As a result, the expression of the affected gene is in most cases enhanced but negative transcriptional regulation is also possible [2].

A plethora of synthetic glucocorticoids is available for therapeutic use. Compared to cortisol, they are characterized by different pharmacodynamic and pharmacokinetic properties. Dexamethasone is by far the most frequently used drug because of its low mineralocorticoid effects and long half-life. Together with other glucocorticoids it has been used in the field of neurooncology since the 1960's [3].

Effects of glucocorticoids on lymphoma cells

The induction of apoptotic cell death in lymphoid cells by glucocorticoids has been recognized several decades ago. This process comprises DNA fragmentation and appears to be independent of wild-type p53 activity [4-6]. Induction of apoptosis might be associated

with reduced transcriptional activity of nuclear factor of activated T cells (NFAT), the induction of glucocorticoid-induced leucine zipper (GILZ) and primarily dependent on the repressive function of the glucocorticoid receptor [7-9]. Furthermore, glucocorticoid-induced cell death may require the presence of glycogen synthase kinase (GSK)-3 [10, 11**]. More recent findings demonstrate the induction of autophagy, an alternative mode of cell death, in lymphoid cells as the main function of glucocorticoids [12]. This process involves the functional activity of Beclin-1, a key regulator protein in autophagy [13**]. Resistance to glucocorticoids partially results from mutations in the glucocorticoid receptor gene, deficient control of its expression or high levels of Bcl-2 [14, 15].

Because of their striking activity, glucocorticoids are commonly used in the treatment of lymphomatous lesions in the central nervous system (CNS). They have been included in almost all chemotherapy protocols for lymphoid malignancies but can also temporarily be administered alone. Dexamethasone, the standard drug, is generally applied in initial doses of 4 to 16 mg per day. Because of unwanted side effects (see below), high doses should only be administered for a short period of time. Since lymphomatous neoplasms will respond rapidly to glucocorticoids and thus obscure a definitive diagnosis [16, 17], patients with suspicion of lymphoma should rather be treated with osmotic agents to reduce intracranial pressure until the diagnosis has been established [18]. Further, tumor remission in response to glucocorticoid administration is only temporary in most patients and must therefore be followed or accompanied by other chemotherapeutic agents.

Effects of glucocorticoids on other tumor cells

In CNS neoplasms other than lymphomas, the effects of glucocorticoids are much more controversial. Several *in vitro* studies suggest that dexamethasone and other steroids are inhibitors of cellular proliferation and may also induce cell death at high concentrations.

Administration of glucocorticoids to glioma-bearing animals was accompanied by prolonged survival in some reports [19-22]. In humans, only single reports have described tumor shrinkage in glioblastoma patients after dexamethasone treatment [23]. In contrast, a multitude of studies demonstrated that glucocorticoids lack any significant effect or even stimulate tumor cell growth *in vitro* and *in vivo* [24, 25]. Most importantly, glucocorticoids induce resistance to chemotherapeutic agents in various tumor models including gliomas [26-28]. This effect may partially result from a dexamethasone-induced expression and increased activity of multidrug resistance transporters [29]. The reduced permeability of the blood-brain barrier for chemotherapeutic agents in response to glucocorticoids (see below) may also contribute to this phenomenon *in vivo*. Therefore, steroid administration should be minimized whenever possible prior to chemotherapy in brain tumor patients. Although critically followed in academic neurooncology, glucocorticosteroids are also criticized from the dietary standpoint in the alternative medical field because of their rapid induction of insulin secretion. There is a debate on carbohydrate-restricted diets which are of unproven relevance, but would need a rather restrictive approach to steroids [30].

Effects of glucocorticoids on brain tumor-associated edema

By far the most common indication for the administration of glucocorticoids to brain tumor patients is the need to reduce mass effect secondary to tumor-surrounding edema. This condition is frequently found in a variety of brain tumors, including gliomas, meningiomas and metastases and may be enhanced by cytotoxic therapy such as irradiation and chemotherapy. Treatment with glucocorticoids commonly results in a massive, albeit transient, improvement of the patient's condition [31]. Small doses may be sufficient in many patients, e.g., 16 mg were not superior to 4 mg regarding improvement in Karnofsky performance status in a randomized trial in patients with brain metastases [32]. As with other

actions of glucocorticoids, the mechanisms that cause a reduction of tumor-associated edema are only partially understood. In preclinical animal studies, a reduction of the permeability of the capillary bed within the tumor was reported [33]. Here, the particular effect of steroids on the microvascular permeability of the brain may originate from differential signalling mechanisms in endothelial cells of the blood-brain barrier compared to other tissues [34].

Several experimental *in vivo* models have demonstrated a favourable effect of glucocorticoids on glioma-associated edema [33, 35, 36]. Animal studies also revealed a dexamethasone-induced expression of calcium-activated potassium channels and occludin which may be involved in the regulation of the blood-brain and blood-tumor barrier [37, 38*]. *In vitro* experiments demonstrated reduced vascular endothelial growth factor (VEGF) levels and increased expression of angiopoietin-1 and claudin-5 in response to corticosteroids [39, 40*]. In humans, the availability of brain imaging studies such as magnetic resonance imaging (MRI) and positron emission tomography (PET) has allowed for a better insight in the effects mediated by glucocorticoids on edema. These techniques revealed a decrease in peritumoral water content and reduced tumor capillary permeability after dexamethasone treatment [41-44]. Tumoral perfusion, assessed by MRI, may also predict the imaging response response to glucocorticoids [45*].

Guidelines for the management of brain tumor-associated edema:

Glucocorticoids have been used for the treatment of tumor-associated edema for more than 40 years. This is in sharp contrast to the very low number of clinical studies investigating these effects within randomized trials [32, 46]. However, about 70-100% of patients with intrinsic brain tumors or metastases are treated with steroids, either alone or during cytotoxic therapy [47]. Overall, a variety of individual therapy regimens in terms of dose and duration is used

[48]. Based on the existing literature, the following provides a clinical practice guideline [49, 50]:

In general, dexamethasone is considered the best available drug in order to provide temporary relief from symptoms that are due to an increase in intracranial pressure and edema. No general recommendation can be given for patients with asymptomatic brain tumors. In most cases, glucocorticoids can be withheld. Patients with mild symptoms caused by increased intracranial pressure and tumor-associated edema will benefit from dexamethasone in a starting dose of 4-8 mg per day. Higher doses of dexamethasone such as 8-16 mg per day are indicated in patients suffering from more pronounced or even severe symptoms related to mass effect. A dose higher than 16 mg per day may be administered upon individual evaluation. However, additional benefit is only rarely observed in few patients based on the clinical experience of the authors and others [51]. It should be considered that phenytoin, a commonly used anticonvulsant, or many other CYP450 targets may reduce the bioavailability of dexamethasone and therefore require an adjustment of the dosage of the glucocorticoid [52, 53].

No concluding guidelines can be given for the prophylactic use of steroids during radiotherapy of patients with primary or secondary brain tumors. Asymptomatic patients may remain free of glucocorticoids, and only a minority of the patients will require dexamethasone with doses ranging from 4-16 mg per day during irradiation. At present, corticosteroids are probably still overused in this indication and small doses may be sufficient in many patients [48, 54, 55*, 56]. Various heterogeneous treatment schedules have been used. In general, because of its long half-life of 36-54 h, dexamethasone can be administered as a once-daily dosing in the morning [32, 54]. While steroids are required and effective during radiotherapy, they are probably ineffective in the management of delayed radiation-induced neurotoxicity [57]. The duration of glucocorticoid treatment should always be adapted to individual needs. Dose reductions should be considered after 7-10 days of administration [47, 54, 58].

Tapering and withdrawal

There are no universally valid guidelines for the tapering of dexamethasone or other glucocorticoids. In most cases, a tapering schedule comprising 2 to 4 weeks might be appropriate but longer periods should be considered for patients who have been using steroids for several months [32, 47, 48].

Long-term administration of steroids, especially when given in high doses, goes along with secondary adrenal insufficiency. Prolonged intake of glucocorticoids can even lead to adrenal gland hypotrophy that may need a recovery period of several months after discontinuation of the exogenous glucocorticoid.

Abrupt disruption or too rapid tapering of glucocorticoid therapy can be accompanied by a lack of endogenous corticosteroids. This is of particular importance in situations with increased glucocorticoid demand such as fever and physical stress. It may result in unspecific complaints such as nausea, headache, myalgias and symptoms of hypotension. In case of suspected hypocortisolism, the hormones of the hypothalamic-pituitary-adrenal axis can be assessed by laboratory tests. Slower tapering schedules will provide relief of symptoms in many patients. Manifest hypocortisolism should be substituted with hydrocortisone. Most patients require a dose in the range of 15-25 mg per day. In order to mimic the circadian cortisol secretion, one half to two thirds of the total daily dose should be administered in the morning [59, 60]. The exact dose must be individually adapted based on clinical symptoms and laboratory parameters such as electrolyte levels.

Side effects of glucocorticoid therapy

Treatment with synthetic glucocorticoids is commonly associated with considerable undesired effects that can be linked to the physiological function of these hormones. While some effects are only observed after steroid intake for weeks or even months, other unwanted aspects of glucocorticoid treatment may become apparent within days. The following gives an overview on the most common and partially threatening side effects:

Steroid-induced diabetes

Glucocorticoids – as the name suggests – increase blood sugar levels by different mechanisms including the mobilization of glucose from the liver and the induction of gluconeogenesis. Elevated serum glucose levels are observed in up to 50% of patients receiving glucocorticoids [47]. Although many patients suffering from primary or secondary brain tumors face a limited life expectancy of few years or even less, the short- and long-term complications associated with diabetes must be taken in account. Furthermore, hyperglycemia may be associated with shorter survival in glioblastoma patients [61**]. Therefore, a regular determination of blood sugar levels is warranted and for patients with prolonged hyperglycemias a temporary therapeutic intervention (e.g. with insulin) should be established.

Steroid myopathy

Myopathy is commonly seen in patients taking glucocorticoids, especially after long-term therapy. It occurs in up to 50% of all patients requiring prolonged steroid use and is more commonly associated with the administration of fluorinated steroids [62, 63]. Clinical features include proximal and symmetrical muscle atrophy and weakness that may affect both upper and lower extremities. The underlying mechanisms have only been partially clarified but glucocorticoid-induced apoptosis in skeletal muscle cells may represent the most important cause [64, 65]. Myofibrillar protein degradation as a result of glucocorticoid-dependent stimulation of the proteasomal activity and suppression of insulin-like growth factor (IGF)-1

signalling in muscle cells may also contribute to muscle atrophy [66-68]. If prolonged treatment with glucocorticoids is indispensable, physical therapy is recommended in the absence of other available specific prevention measures [69].

Osteoporosis

Long-term administration of glucocorticoids is frequently associated with osteoporosis which results in significant morbidity and mortality [70, 71]. The underlying pathophysiological mechanisms include the induction of apoptosis in osteoblasts and osteocytes [72] and a reduction of cytokine-dependent osteoblast differentiation [73**]. The effects of steroids on bone loss and increased fracture risk are dose-dependent. Particular attention should be paid to patients receiving other osteoporosis-promoting drugs such as loop diuretics or thyroxine. Special attention should also be given to individuals using medications that increase the risk of falling including antihypertensives, some anticonvulsants and benzodiazepines [74]. Bisphosphonates can be used for the prevention of fractures, especially in patients with longer life expectancy. These agents inhibit bone resorption by binding to bone mineral followed by a decreased activity of the osteoclasts. Teriparatide, a synthetic fragment of human parathyroid hormone, stimulates new bone formation and is available as a second-line option [75-77]. Patients receiving glucocorticoids should also be endowed with calcium (800-1200 mg per day) and vitamin D supplements (> 800 IU per day) [78-80].

Other side effects:

Treatment with glucocorticoids may affect electrolyte levels in the blood. Special attention must be given to decreased potassium levels that may reach life-threatening dimensions [81]. Timely oral substitution will prevent significant electrolyte disturbances in the majority of cases. Other side effects attributed to glucocorticoid therapy include psychiatric disorders such as anxiety, depressive disorders, insomnia and increased appetite. Administration of

glucocorticoids can also result in a marked suppression of the immune system leading to an increased risk for infections such as *Pneumocystis jirovecii* pneumonitis (PJP, formerly known as *Pneumocystis carinii* pneumonitis, PCP) [82, 83]. Despite the lack of general guidelines, it might be warranted that all patients receiving radio- and/or chemotherapy with concomitant steroid use and all patients with CTCAE grade 3 or 4 lymphopenia should obtain prophylactic treatment with trimethoprim-sulfamethoxazole or aerosolized pentamidine [69, 84, 85]. In order to avoid gastrointestinal side-effects due to peptic ulcers or even bleedings, the prophylactic administration of proton pump inhibitors, H2 blockers or antacids should be considered. Steroid cataract and peripheral edema have also been frequently reported in patients taking glucocorticoids [32, 47, 48, 58].

Unfortunately, no convincing alternative agents that might replace glucocorticoids are available. The phytotherapeutic agent H15 contains boswellic acids and may reduce tumor-surrounding edema in the brain and therefore allow for a reduction of the steroid dose. However, it has only limited activity and has only been assessed in small clinical studies [86]. In modern neurooncology, anti-VEGF agents, such as bevacizumab, which is registered in the USA for recurrent glioblastoma [87**] and is in clinical trials for the newly diagnosed situation may - amongst a true anti-tumor effect, which is under debate - replace steroids when used for treatment. Animal experiments show that brain tumor-bearing mice survive longer because of the marked anti-edematous action of the VEGF receptor tyrosine kinase inhibitor cediranib, although the tumor cells proper are basically unaffected by the treatment [88**].

Conclusion

The beneficial effects of corticosteroids on different pathological conditions place them in an outstanding position in the treatment of neurooncological patients. Most importantly,

glucocorticoids provide temporary relief from symptoms related to increased intracranial pressure and edema in consequence of primary and secondary brain tumors. They also remain a substantial part in the treatment of patients suffering from lymphoma manifestations in the CNS. Because of their side effects and multiple interactions with other treatment modalities, they should be used with caution, and the side effects should be recognized in time.

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